# Design and implementation of the North American Pediatric Cardiomyopathy Registry

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The Pediatric Cardiomyopathy Registry (PCMR) was established to describe the epidemiologic features and clinical course of selected cardiomyopathies in patients aged 18 years or younger and to promote the development of etiology-specific treatments. Sixty-one private and institutional pediatric cardiomyopathy practices in the United States and Canada were recruited to participate in the PCMR. The registry consists of a prospective, population-based cohort of patients in 2 regions (New England and the Central Southwestern United States) and a retrospective cohort of patients diagnosed between 1991 and 1996. Annual follow-up data are collected on all patients. As of June 1999, the PCMR consisted of 337 prospectively identified and 990 retrospectively identified patients. The PCMR has demonstrated the feasibility of establishing a large database of sociodemographic and clinical information on children with pediatric cardiomyopathy. Through this cooperative effort, the PCMR will obtain precise estimates of the incidence of pediatric cardiomyopathy and a better understanding of the natural history of this disease. (Am Heart J 2000;139:S86-S95.)

Cardiomyopathy is an uncommon and potentially devastating disease in infants and children. It accounts for only 1% of pediatric cardiac disease but can lead to significant morbidity and death.[1] Nearly one third of children die after 1 year and a large proportion of those who survive are left with permanent myocardial damage and dysfunction.[1]

Despite its impact on mortality, the rate of occurrence of cardiomyopathy in the pediatric population is not well defined, and its natural history remains incompletely understood. To date, there have been several natural history studies of cardiomyopathy in infants and children but few population-based studies describing its epidemiologic characteristics.[2-22] These studies are limited by small sample sizes or ethnically homogeneous populations of children. A population-based study of all cases of idiopathic cardiomyopathy in Olmsted County, Minnesota, lacked a sufficient number of children to provide reliable estimates of incidence across all age groups.[20] There did, however, appear to be an increase in the incidence of pediatric cardiomyopathy over the duration of the study (from 1975 to 1984).[20] The largest population-based studies of pediatric idiopathic cardiomyopathy were conducted in Finland and Australia.[21,22] These studies reported an annual incidence of 0.65 per 100,000 in persons 20 years old or younger residing in Finland and 1.09 per 100,000 in children 10 years old or younger residing in Australia. Similar to the Olmsted County study, the Finnish study observed a trend toward an increase in cases of dilated cardiomyopathy from 1980 to 1991. To our knowledge, there have been no large, population-based epidemiologic investigations of pediatric cardiomyopathy in North America. Furthermore, data from studies examining the natural history of pediatric cardiomyopathy suggest that the cause of reported cases is largely unknown, the prognosis is poor, and treatment modalities remain nonspecific and palliative.[1-18]

Because of the paucity of data on the epidemiologic features of cardiomyopathies in pediatric populations and the need to better understand causes and develop treatments, we sought to establish a registry of a large cohort of children with cardiomyopathy residing in the United States and Canada. The Pediatric Cardiomyopathy Registry (PCMR) was designed to describe the epidemiologic characteristics and clinical course of selected cardiomyopathies in patients aged 18 years old or younger and promote the development of etiology-specific prevention and treatment strategies. In this report, we describe the design and implementation of the National Heart, Lung and Blood Institute–sponsored PCMR of North America. This article describes the creation of the registry and some of its characteristics. Further data from the PCMR will be published in the future.

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*0002-8703/2000/$12.00 + 0* **4/0/103933**

**Table I.** Aims of the PCMR

| |
|---|
| Specific |
| To estimate the annual incidence of pediatric cardiomyopathy in selected regions in the United States and Canada. |
| To determine the annual incidence of pediatric cardiomyopathy with respect to sociodemographic characteristics of the population. |
| To monitor trends in the incidence of pediatric cardiomyopathy with respect to geographic area and sociodemographic characteristics of the population. |
| To determine the overall survival experience of patients diagnosed with pediatric cardiomyopathy in the United States and Canada and in selected geographic areas. |
| To determine the survival experience of patients diagnosed with pediatric cardiomyopathy with respect to selected sociodemographic characteristics and treatment methods. |
| To describe clinical manifestations, clinical course, and morbidity associated with pediatric cardiomyopathy. |
| Clinical |
| To elucidate the causes and pathophysiologic characteristics of pediatric cardiomyopathy. |
| To coordinate and encourage multicenter, collaborative clinical studies and trials on the basis of registry data and to assess therapeutic and preventive efforts aimed at the primary defects that result in specific forms of pediatric cardiomyopathy. |
| To educate medical professionals about the epidemiologic, molecular, and genetic basis of pediatric cardiomyopathy by disseminating information derived from registry data. |

# Methods

## Organization

The PCMR was funded under an investigator-initiated research award by the National Heart, Lung, and Blood Institute during the period September 1, 1995, to August 31, 1999. Under this funding mechanism, there was a primary grant awardee, the University of Rochester, New York, that subcontracted to 4 additional coordinating institutions: Boston Children's Hospital; Texas Children's Hospital, Houston; New England Research Institutes, Watertown, Massachusetts; and Albany Medical College, New York. These 5 key institutions collaborated in the design, protocol development, and implementation of the PCMR.

The University of Rochester served as the Administrative Coordinating Center responsible for the overall direction of the registry, coordination of activities among the 5 centers, and data collection at the participating clinical centers (see Appendix). The Boston Children's and Texas Children's hospitals served as Clinical Coordinating Centers and were responsible for accrual of data in their regions and for clinical quality assurance activities. As the Data and Statistical Coordinating Center, New England Research Institute was responsible for data management activities and statistical analyses and coordinated the development of data forms and the study manual of operations. A statistical consulting site was established at the Brigham and Women's Hospital. A senior medical consultant was established and available for direction at the Albany Medical College. A Steering Committee, composed of the principal investigators and co-investigators from each of the 6 institutions, served as the decision-making body for the study. Members participated in monthly conference calls to review the study timeline, status of data collection, data quality assurance issues, and statistical analyses. In addition, a Scientific Advisory Council was formed to advise the Steering Committee and assisted in the overall development and direction of the PCMR.

## Design

The PCMR was designed to address the specific clinical and epidemiologic aims outlined in Table I. Specifically, the goals of the registry were to define the incidence and clinical course of pediatric cardiomyopathy, both overall and in demographic subgroups. To achieve these objectives, we established 2 cohorts of patients with cardiomyopathy: a population-based cohort of newly diagnosed patients residing in 2 geographically distinct regions of the United States (New England and the Central Southwest) and a retrospective cohort of patients recruited primarily from selected large tertiary care centers in the United States and Canada. Patients in the population-based cohort were identified concurrently with their diagnosis; cases were eligible for inclusion if diagnosis was made on or after January 1, 1996 (the approximate date of initiation of enrollment for the registry). Patients in the retrospective cohort were identified from a review of medical records; patients were eligible for inclusion if diagnosed with cardiomyopathy between January 1, 1990, and December 31, 1995. The former approach provided an adequate sample to calculate precise estimates of incidence rates. The latter approach allowed for the efficient accrual of a large sample of cases with adequate follow-up to study the natural history of cardiomyopathy. Specifically, we estimated approximately 1000 patients in the retrospective cohort would provide adequate power to make meaningful comparisons of clinical outcomes, such as survival and heart transplantation, between selected subgroups of interest. All patients enrolled in the registry were monitored prospectively from their date of diagnosis through August 31, 1999. Participating institutions and clinical centers obtained approval from their institutional review boards for human subjects.

**Table II.** PCMR exclusion criteria

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|---|
| Older than 18 years of age at time of diagnosis |
| Endocrine disease known to cause heart muscle disease (including infants of diabetic mothers) |
| History of rheumatic fever |
| Toxic exposures known to cause heart muscle disease (eg, anthracyclines, mediastinal radiation, iron overload, heavy metal exposure) |
| HIV infection or born to an HIV-positive mother |
| Kawasaki disease |
| Congenital heart defects unassociated with malformation syndromes (eg, valvular heart disease, congenital coronary artery malformations) |
| Immunologic disease |
| Invasive cardiothoracic procedures or major surgery during the preceding month, except those specifically related to cardiomyopathy, including LVAD, ECMO, and AICD placement |
| Uremia, active or chronic |
| Abnormal ventricular size or function that can be attributed to intense physical training or chronic anemia |
| Chronic arrhythmia, unless inclusion criteria before the onset of arrhythmia can be documented (a patient with chronic arrhythmia, subsequently ablated, whose cardiomyopathy persists after 2 months is not to be excluded) |
| Malignancy |
| Pulmonary parenchymal or vascular disease (eg, cystic fibrosis, cor pulmonale, pulmonary hypertension) |
| Ischemic coronary vascular disease |
| Association with drugs known to cause hypertrophy (eg, growth hormone, corticosteroids, cocaine) |

*LVAD,* Left ventricular assist device; *ECMO,* extracorporeal membrane oxygenation; *AICD,* automatic interventricular cardioversion device.

## Patient eligibility and case definition

Patients aged 18 years old or younger with a newly diagnosed cardiomyopathy who underwent diagnostic evaluation at a participating clinical center were eligible for inclusion in the PCMR. Cases diagnosed at autopsy were also eligible for inclusion, although pathology departments and local medical examiners' offices were not officially queried in this study. Patients in the population-based cohort had to reside within the boundaries of the geographic regions of the registry, as defined by their zip code. Patients with any of the secondary causes of cardiomyopathy shown in Table II were excluded. The cases included in the PCMR were primarily idiopathic cardiomyopathy as well as cardiomyopathy caused by metabolic, genetic, or neuromuscular disorders and infections. An algorithm-based clinical approach to genetic cardiomyopathy in children was developed to assist participating cardiologists in the determination of specific causes.[23] Its use was not compulsory for participation in the PCMR.

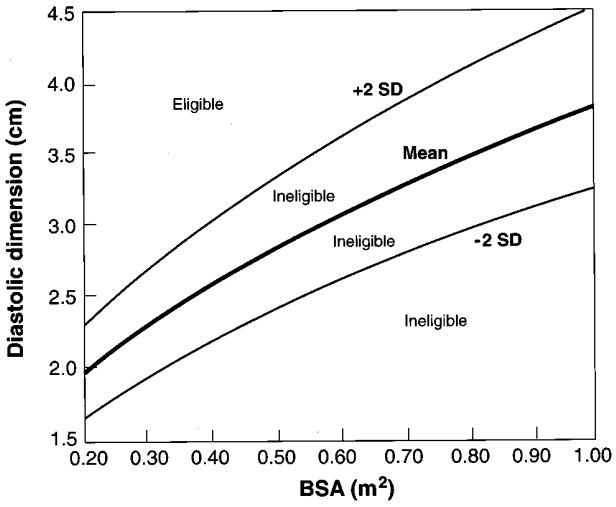
Definite cases of cardiomyopathy had to meet precise echocardiographic measurements (Figures 1 through 3) and semiquantitative patterns (Table III) or have biopsy-proven cardiomyopathy. Patients with a physician's diagnosis of cardiomyopathy who did not meet these strict echocardiographic criteria were still included in the registry as probable cases of cardiomyopathy. Children who did not have a diagnosis of cardiomyopathy but had family members diagnosed with cardiomyopathy or had conditions that might predispose them to cardiomyopathy (such as Duchenne's muscular dystrophy and myocarditis) were enrolled for purposes of prospectively following the development of cardiomyopathy.

## Data collection approach

Initially, the PCMR depended on voluntary submission of data from participating clinical centers. Each participating practice was asked to identify a single contact person at their site, the local PCMR coordinator, who would be responsible for the identification and enrollment of cases and all data collection activities. Data were abstracted from patients' medical records onto hard copy forms and mailed directly to the PCMR Data and Statistical Coordinating Center for data entry. Participating clinical centers were reimbursed $25 per data form completed. Other incentives for participation included a quarterly informational PCMR newsletter and presentations at symposia and national meetings, where active participation was encouraged. The advantage of this voluntary data collection system was its relatively low cost. Its limitations included potential underreporting of cases and delays in enrolling patients and completing data forms.[24] An active system of data collection was instituted to supplement voluntary data submission after the first year of implementation of this protocol because of delays in patient enrollment and data submission. An outreach team of full-time data collectors was established and based at the Administrative Coordinating Center and one regional Clinical Coordinating Center (Boston Children's Hospital). This team traveled to the participating clinical centers to complete the enrollment of new cases and abstract relevant data from patients' medical records at regular intervals during the study.

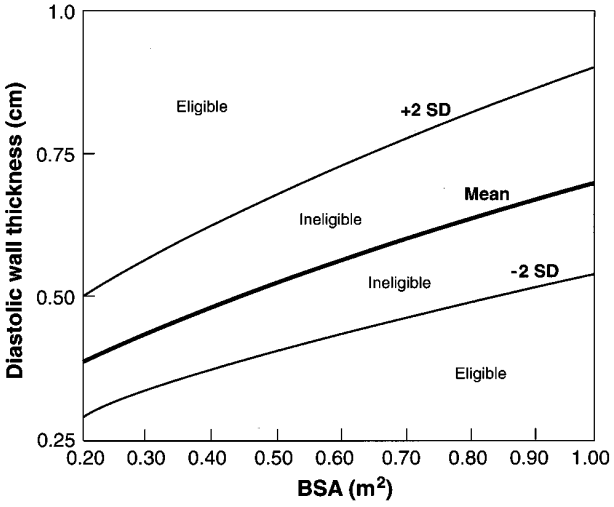
This active effort immediately increased PCMR enrollment (Figure 4). Although somewhat more costly, it led to more timely and more complete data collection and the potential for a more standardized interpretation

**Figure 1**




Echocardiographic parameters for left ventricular end-diastolic dimension. *BSA,* Body surface area.

**Figure 2**



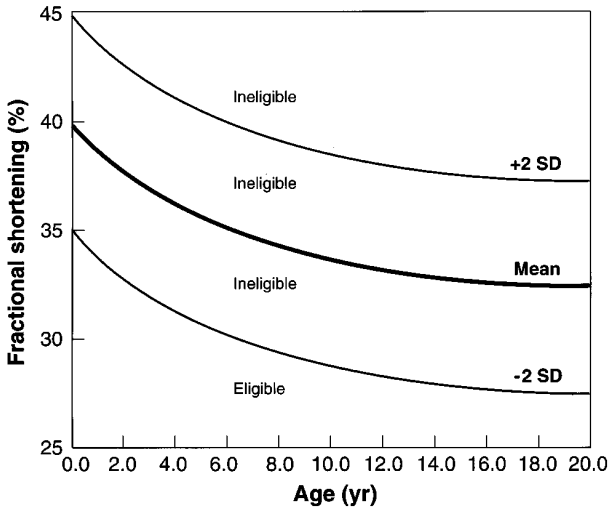

Echocardiographic parameters for left ventricular end-diastolic wall thickness. *BSA,* Body surface area.

of the PCMR protocol. Furthermore, it allowed the study to continue to collect a comprehensive set of data on potential risk factors and patient outcomes, which were required to study the natural history of this disease adequately. For example, variables collected on the retrospective cohort included date of diagnosis of cardiomyopathy, age, sex, race/ethnicity, functional type of cardiomyopathy according to World Health Organization criteria, family history of cardiomyopathy, results of several relevant laboratory tests and procedures, health care use, drug therapy, surgical management, and vital status. In contrast, only a limited subset of these variables was required and collected for the population-based cohort and used for calculating incidence rates. At present, the majority of data for the PCMR has been collected by the outreach team of data collectors. However, voluntary submission of data by any institution is not prohibited.

## Data collection procedures

Enrollment of patients in the PCMR required completion of a brief self-addressed and stamped postcard with key information on date of diagnosis, study inclusion criteria, demographics, and assignment of a unique study identifier. All patient identifiers were removed from data transmitted to the Data and Statistical Coordinating Center to ensure confidentiality. Identifying information, such as patient names and medical record numbers linking patients to their PCMR identification number, were logged at the corresponding clinical center and accessible only to the local site coordinator. Once a patient was enrolled in the PCMR and eligibility criteria were verified by the

**Figure 3**




Echocardiographic parameters for left ventricular fractional shortening (%).

data management system, supplementary data were collected on the patient's clinical history and results of tests and procedures conducted at the time of diagnosis of cardiomyopathy. Similar information was collected annually thereafter. The data management system automatically generated data forms based on the patient's date of diagnosis and follow-up status. All data forms were labeled at the Data and Statistical Coordinating Center and mailed to the participating clinical centers or PCMR outreach team for comple-

**Table III.** PCMR inclusion criteria for echocardiographic measurements and patterns*

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|---|
| Measurements |
| Left ventricular fractional shortening or ejection fraction >2 SD below the normal mean for age. Fractional shortening is acceptable in patients with normal ventricular configuration and no regional wall motion abnormalities. Abnormal ejection fraction by echocardiography, radionuclide or contrast angiography, or magnetic resonance imaging are acceptable alternatives, but age-appropriate, normal values for the individual laboratory must be used. |
| Left ventricular posterior wall thickness at end diastole >2 SD above the normal mean for body surface area. |
| Left ventricular posterior wall thickness at end diastole >2 SD below the normal mean for body surface area. |
| Left ventricular end-diastolic dimension† or volume >2 SD above the normal mean for body surface area. Dimension data are acceptable under the conditions outlined for fractional shortening, and volume data may be derived from the imaging methods, as in the first item above. |
| Patterns |
| Localized ventricular hypertrophy, such as septal thickness >1.5 times left ventricular posterior wall thickness, with at least normal left ventricular posterior wall thickness, with or without dynamic outflow obstruction. |
| Restrictive cardiomyopathy: one or both atria enlarged relative to ventricles of normal or small size with evidence of impaired diastolic filling and in the absence of significant valvar heart disease. |
| Contracted form of endocardial fibroelastosis, similar to restrictive cardiomyopathy plus echo-dense endocardium. |
| Ventricular dysplasia/Uhl's anomaly: very thin right ventricle with dilated right atrium, usually better assessed by magnetic resonance imaging than echocardiography. |
| Concentric hypertrophy in the absence of hemodynamic cause. |
| Left ventricular myocardial noncompaction: very trabeculated spongiform left ventricular myocardium with multiple interstices. |

*SD,* standard deviation.
*Patients must have at least 2 of the measurements and/or 1 of the patterns specified.
†End-diastolic dimension is largest left ventricular dimension in short-axis view.

tion. Several reports were generated on a monthly basis to monitor the status of enrollment, completion of annual follow-up form, and outstanding edits to forms, both overall and by site.

Photocopies of death certificates and autopsy reports with identifiers removed were also mailed to the Data and Statistical Coordinating Center for central coding. Because of the potential for duplicate enrollment of patients who were evaluated at more than one institution, the data management system set screening parameters to identify patients with identical acrostic code (a 5-digit code comprising the first 3 letters of the last name and first 2 letters of the first name), date of birth, sex, and subtype of cardiomyopathy. Any duplicates were reviewed with the appropriate clinical centers for resolution.

## Clinical center recruitment and patient enrollment

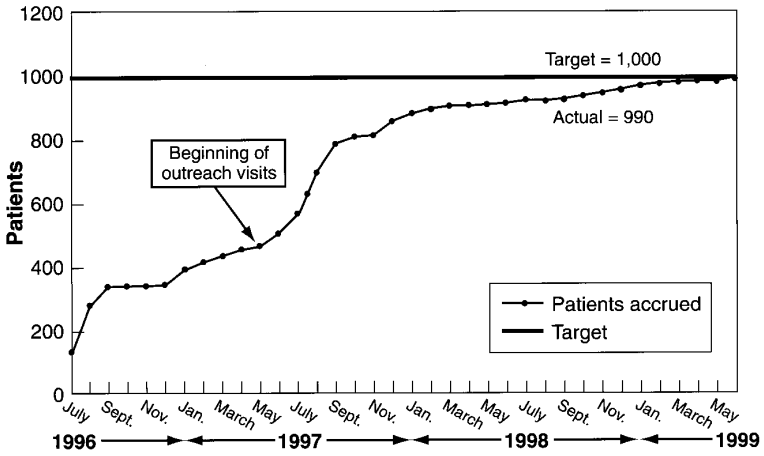
We identified 16 private and institutional pediatric cardiology practices in the New England region (Maine, New Hampshire, Massachusetts, Rhode Island, Connecticut) and 20 practices in the Central Southwest region (Texas, Oklahoma, Arkansas) and contacted the pediatric cardiologists to obtain their support for participation in the PCMR. All 16 of the centers in the New England region and 19 of the 20 centers in the Central Southwest region agreed to participate and enroll patients. One center in the Central Southwest region claimed no cardiomyopathy patients and therefore did not participate in the study. Similarly, we identified and contacted the major institutional pediatric cardiology practices in the United States and Canada to obtain their support for enrollment of patients in the retrospective cohort. Thirty-nine clinical centers in 22 states of the United States and in Toronto, Ontario, agreed to participate.

To date, the PCMR has enrolled 99% (n = 990) of its target sample in the retrospective cohort and 337 patients residing in the New England and Central Southwest regions for the prospective population-based cohort (Figure 4). The majority of these patients met criteria for definite or probable cardiomyopathy as previously defined. Table IV summarizes the most recent follow-up status of all patients enrolled in the PCMR as of June 1, 1999. The majority of patients are alive; only 6% have been discharged from medical care, presumably because of resolution of their symptoms. Loss to follow-up has been substantially higher in the retrospective cohort than in the population-based cohort, 24% and 2%, respectively, presumably because of their retrospective enrollment. The lost to follow-up rate may include patients who died and therefore may be falsely elevated in the retrospective cohort. The impact of increased length of follow-up on lost to follow-up rate cannot be assessed in the current study.

## Quality control

Quality control systems were developed to ensure the accuracy and completeness of data collected for the PCMR. Quality control efforts focused on 2 aspects: patient enrollment and data collection. Our inclusion and exclusion and echocardiographic criteria were the first level of quality control. Our method for determining patient eligibility had clearly defined echocardiographic measurements that could be verified by the data management system. Patients' echocardiographic values

**Figure 4**




Retrospective patients enrolled by month: effects of outreach visits.

in the data management system were compared with previously defined echocardiographic norms (Figures 1 through 3).[25] If the patient's values did not meet the study inclusion criteria, the data were reviewed by the PCMR cardiologists and a final determination of eligibility was made. Edit reports (reports generated to specifically query the institution about missing data or imprecise data that fell out of the expected range of values) were sent to the individual clinical centers for resolution. An additional level of quality control was self-contained within the data collection forms: built-in redundancies to substantiate the data contained therein.

In the initial period, when data submission was entirely voluntary and training of data collectors was not feasible, detailed operations manuals were developed for each participating clinical center to ensure standard implementation of the PCMR protocol. The transition to a primarily active data collection system provided the opportunity to establish staff requirements and train and monitor data collectors. All traveling PCMR data collectors, or registrars, were required to have a minimum of a baccalaureate degree and undergo an intensive 2-day training seminar in data abstraction from medical records. They were trained in medical terminology and purposes of various cardiac procedures and tests, such as electrocardiograms, Holter monitors, cardiac catheterization and biopsy, classification of cardiomyopathies, inclusion and exclusion criteria, graphic interpretation of echocardiographic parameters, and data form completion. The PCMR registrars had telephone and sometimes personal access to the designated cardiologist at each clinical center during their visit to collect data. Any questions about data interpretation or inclusion and exclusion criteria were discussed with the PCMR cardiologist.

**Table IV.** Current status of patients

| | Retrospective cohort* | Prospective population-based cohort† |
|---|---|---|
| Alive | 605 (61%) | 294 (87%) |
| Dead | 153 (15%) | 36 (11%) |
| Lost to follow-up | 232 (23%) | 6 (2%) |
| Total | 990 (100%) | 337 (100%) |

*Patients diagnosed with cardiomyopathy from 1990 to 1995.
†Patients diagnosed with cardiomyopathy from 1996 to 1998.

## Finances

The PCMR was supported by National Institutes of Health grant HL53392 and the Parker Family Foundation. There are presently 9 employees, 3 subcontractors, and 2 consultants. Participating PCMR centers were reimbursed for their efforts at a rate of $25 per form completed, for a total of $30,000 per year. Travel for 5 registrars totaled approximately $50,000 per year. Approximately three quarters of PCMR data were collected by the traveling registrars.

## Discussion

The PCMR has established the largest database of sociodemographic and clinical information on children diagnosed with cardiomyopathy at private and institutional pediatric cardiology practices throughout the United States and Canada and has demonstrated the feasibility of this cooperative effort. With this large sample and extended follow-up, we will be able to calculate precise estimates of the incidence of pediatric car-

diomyopathy and to understand better its natural history. Furthermore, this registry may be used as the basis for future etiologic or diagnostic studies and clinical trials of therapies for pediatric cardiomyopathy. Some examples include studies of metabolic and mitochondrial disease as causes of cardiomyopathy, use of diagnostic modalities such as positron emission tomographic scanning, and studies of treatment modalities such as β-blockade. Etiology-specific modalities are imperative to the development of more efficacious treatment of pediatric cardiomyopathy.

A fundamental consideration in the design and implementation of the PCMR was the use of a voluntary (or passive) versus active data collection approach. We found that active data collection by trained PCMR staff resulted in more timely and complete data submission and may have contributed to an improvement in the quality of the data submitted. Currently, our data collection efforts have resulted in completion of more than 90% of the annual follow-up forms expected on patients enrolled in the study. Future plans for the registry include the development of an Internet-based data management system to facilitate timely and voluntary patient enrollment at the clinical centers. In addition, the potential for patient loss to follow-up requires attention. Patients diagnosed with disease in the distant past are more likely to have missing records or medical care that cannot be tracked to the present.[26] In our registry, the lost to follow-up rate for the retrospectively identified cases, although acceptable, was 10-fold higher than the rate for those identified concurrently with their diagnosis. This issue cannot be adequately addressed at this time.

Our study has some limitations. The incidence of cardiomyopathy may potentially be underestimated because children with sudden death as their presenting symptom may be enrolled in the PCMR at autopsy but may not be readily identified because departments of pathology and medical examiners' offices are not specifically queried in the present protocol.[27] Similarly, infants and children with asymptomatic left ventricular dysfunction do not seek medical evaluation and therefore cannot systematically be identified or enrolled in the registry. Studies have observed a 50% 7-year mortality rate in adults with asymptomatic left ventricular dysfunction, implying that this condition may have some prognostic significance.[28] Future goals of the registry will be to develop approaches to evaluate complete case ascertainment and to include cases that are first seen at the patient's death, possibly by reviewing records at the clinical center's division of pathology, local health departments, and coroners' offices.

The PCMR has gathered the information necessary to understand the diagnosis, treatment, and outcomes of this potentially devastating disease. Because of its high quality, large size, and completeness, this database provides a foundation for many future studies of cardiomyopathy in children that are likely to improve the overall outcome for patients with this disease.

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# Appendix

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